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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/425,075	10/21/1999	PRABHAKARA V. CHOUDARY	480.97-1-(HV	9044

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	35

DATE MAILED: 07/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/425,075	CHOUDARY ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *34* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1. The request filed on 5/13/02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/425,075 is acceptable and a RCE has been established. Claims 36-49 are pending and are currently under prosecution. An action on the RCE follows.

2. Claims 22 and 25-32 have been canceled.

Claims 36-49 have been added.

3. Claims 36-49 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be foound in a prior Office Action

5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (Proc. Natl. Acad. Sci. USA 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-19 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96) and Sambrook et al (Molecular Cloning, A Laboratory Manual Second Edition pages 1.85, 12.16-12.20, and 13.42-13.44, 1989) is withdrawn in view of the amendments to the claims.

7. The rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al and further in view of The 1997 Invitrogen Catalog is withdrawn in view of the amendments to the claims.

8. The rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (PNAS 85:8678-8682, 1988) as applied to claims 22-24 above, and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-19 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96), Sambrook et al (Molecular Cloning, A Laboratory Manual Second Edition pages 1.85, 12.16-12.20, and 13.42-13.44, 1989) and Vanderlaan et al (U.S. Patent 5,429,925, issued 7/4/95) is withdrawn in view of the amendments to the claims.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 103

9. Claims 36-40 and 42-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (Proc. Natl. Acad. Sci. USA 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-17 and

Master Catalog Amendment Notice for pPICZ vectors from 4/15/96) and Robinson et al (U.S. Patent 6,204,023, filed 6/6/95).

The claims encompass a method for production of an antibody that binds antigen comprising culturing a recombinant Pichia pastoris SMD1168 cell comprising a vector comprising a first and second expression cassette wherein the first cassette comprises a Pichia alcohol oxidase promoter and a S. cerevisiae α-factor signal sequence and a second expression cassette comprising the same promoter and signal sequence as the first cassette and culturing and harvesting the antibody wherein the antibody is recovered at more than about 10mg/l wherein the antibody is a humanized antibody. Further claimed is the vector and Pichia cell.

Horwitz et al teach a method for the production of an antibody in S. cerevisiae yeast cells with the vectors comprising cDNA encoding for an antibody, a promoter and transcription terminator, and signal sequence (see abstract and page 8679 and figure 2). Horwitz et al does not teach a recombinant host P. pastoris, SMD1168 transformed with a vector for expression with dual expression cassettes, the Pichia alcohol oxidase promoter, alpha factor signal sequence, AOX1-P promoter, . These deficiencies are made up for in the teachings of Cregg et al , the Invitrogen 1997 Catalog, and Robinson et al.

Cregg et al teach production of foreign proteins in Pichia pastoris with the promoter AOX1.

Robinson et al teach methods of expression of antibodies in yeast with expression plasmids comprising the light chain and heavy chains each attached to a

yeast promoter and terminator and are placed on the same plasmid (see column 16, lines 15-20) and yeast is a preferred host because yeast provides substantial advantages for the production of immunoglobulin light and heavy chains because yeast carry out post-translational peptide modifications including glycosylation and a number of recombinant DNA strategies exist which utilize strong promoter sequences and high copy number plasmids which can be used for overt production of the proteins in yeast (see column 15, lines 39-45).

The Invitrogen 1997 Catalog teach high copy number vectors for expression of proteins in P. pastoris SMD1168 and the vectors comprises the inducible AOX1 promoter, a poly cloning site comprising EcoRI, BsmBI, BglII, and BamHI, the alpha-factor signal sequence, and the vector is designed for antibody expression.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for production of an antibody in P. Pastoris comprising a vector comprising a first and second expression cassette in view of Horwitz et al, Cregg et al, Robinson et al, and the 1997 Invitrogen Catalog in order to produce antibodies in P. pastoris.

One of ordinary skill in the art would have been motivated to produce the claimed method and vectors and host cell because Horwitz et al teach recombinant production of proteins, specifically, an antibody in S. cerevisiae in general with selection, screening, and purification and testing antigen binding. In addition, one of ordinary skill in the art would have been motivated to produce the claimed method and vectors and host cell in P. pastoris because Cregg et al teach production of heterologous proteins in P. pastoris

overcomes the problems associated with producing commercially useful levels of proteins in S. cerevisiae (see page 33, introduction) and the P. pastoris is ideally suited for the production of many heterologous proteins due to the fact that (1) a detailed understanding of the growth characteristics of the organism in high-density fermentors is known, (2) the ability to place foreign DNA into the genome in a precisely controlled manner, and (3) promoters are tightly regulated and efficiently transcribed to produce proteins at high levels. (See page 40). In addition, one of ordinary skill in the art would have been motivated to produce the claimed method and vectors and host cells because the Invitrogen Catalog teach a Pichia expression vector called pPICZ which is based on homologous recombination comprising; several restriction sites for cloning of recombinant proteins, a promoter (AOX1), termination sequences, selectable markers (zeocin), and alpha-factor secretion signal for expression in P. pastoris of antibodies and the vector is designed for production of proteins as high as grams per liter (see pages 14-15 and 18). Moreover, one of ordinary skill in the art would have been motivated to produce the claimed method and vectors and host cells because Robinson et al teach production in yeast of chimeric or humanized antibodies using a vector with both a light chain and a heavy chain linked to promoters and terminators in a single plasmid and the vectors can further comprise yeast leader sequences for antibody secretion (see columns 15-16).

Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because Horwitz et al teach the antibodies produced in yeast were secreted

and functional by binding the target antigen (see abstract). In addition, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because Cregg et al teach the result of the engineered yeast is a yeast that is "easily scaled up from shake-flask to large-volume, high-density cultures with little change in the kinetics of product synthesis" (see abstract) Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because the Invitrogen Catalog teach that the expression vector and P. pastoris makes "an ideal tool for laboratory research as well as industrial applications" (see page 14).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

10. Claims 36-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (PNAS 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-19 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96), Robinson et al (U.S. Patent 6,204,023, filed 6/6/95) and Vanderlaan et al (U.S. Patent 5,429,925, issued 7/4/95).

Claims 36-40 and 42-49 have been described supra. Claim 41 recites wherein the antibody binds dioxin.

Horwitz et al has been described supra. What Horwitz does not teach has been described supra and in addition Horwitz does not teach an antibody which specifically binds dioxin. The deficiencies of Horwitz et al is made up for in the teachings of Cregg et al , the Invitrogen 1997 Catalog, Robinson et al, and Vanderlaan et al.

Cregg et al , the Invitrogen 1997 Catalog, and Robinson et al have been described supra.

Vanderlaan et al teach the anti-dioxin antibody DD1.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for production of an anti-dioxin antibody from the DD1 hybridoma in Pichia with an expression cassette comprising a light and heavy chain in view of Horwitz et al, Cregg et al , the Invitrogen 1997 Catalog, Robinson et al, and Vanderlaan et al in order to produce the antibody in Pichia.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the claimed method with an anti-dioxin antibody in Pichia because Horwitz et al, Cregg et al , the Invitrogen 1997 Catalog, and Robinson et al provide motivation and reasonable expectation of success as stated above in the above rejection and it would have been obvious to produce high levels of expression of the anti-dioxin antibody of Vanderlaan et al because the anti-dioxin antibody "permits detection of dioxin contaminants in industrial environmental samples" and it would be obvious to produce large amounts of an antibody needed to analyze many samples.

Response to Arguments

11. The response filed 5/13/02 with regards to the rejections of record directed to the 103(a) rejections was found persuasive because the prior art of record did not teach a dual expression cassette, however, the NEW GROUNDS of rejections provide this element in the rejection based on the amendments to the claims. The response states that there would not be any reasonable expectation of success in expressing two subunits of an antibody using one vector because of problems with transcription, translation, and intramolecular recombination (see page 6 of response). In response to this argument, the art of Robinson et la clearly suggests and states that expression of an antibody with a single expression cassette is feasible.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D., whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879